Advisory Panel Questions

1. The submitted preclinical data demonstrate that ProGEL Surgical Sealant clears rapidly from rats and pigs. For example, over 50% of a ^{14}C-labeled device was excreted after 24 hours and virtually all radio-activity was recovered from rats at 14 days post-implant. The Sealant was also largely absent at 4 days with only isolated fragments of the Sealant apparent at 7 days after implantation on pigs' lungs.

In the randomized (2:1 ratio) controlled, multi-center study in which 103 patients were treated with ProGel Surgical Sealant and 58 received Control treatment, 32 (33%) of the ProGel Lung Sealant and 12 (22%) of the Control patients had partial lung expansion at 30 days post-surgery.

In an independent radiologist's assessment of CXRs from a subset of study subjects:

- the incidence of complete lung expansion in the recovery room was similar for both treatment groups (i.e., 72% for ProGEL Surgical Sealant (n=36) and 70% for Control (n=20) patients);

- the incidence of complete lung expansion was (20/39 - 51%) for ProGel Surgical Sealant as compared to the Control (8/20 40%) patients on the day of chest tube removal.

- at 30 days post-surgery, Control (20/20 100%) patients displayed a larger numerical, but not statistical (p=0.078), occurrence in the incidence of completely expanded lungs compared to ProGel Surgical Sealant (6/36 83%) patients; and

- the median size of pneumothorax in Sealant patients increased from 21 mm at the time of chest tube pull (n=19) to 27 mm at 30 days after surgery (n=6). In contrast, all pneumothorax in Control patients had resolved.

Please discuss the clinical significance of these findings and their impact on the clinical safety and effectiveness of ProGel Surgical Sealant as an adjunct to standard care, compared to control, (i.e., standard care alone).

2. ProGel Surgical Sealant is comprised of two main components, (i.e., a bi-functionalized polyethylene-glycol cross-linker and human serum albumin). Clearance studies with ^{14}C-labeled Sealant implanted in rats revealed that urine was the primary route of excretion (70%) with the majority of clearance occurring within 1-3 days after implantation. In a second study over 50% of the ^{14}C-labeled device was excreted after one day and virtually all radio-activity was recovered from rats by 14 days after implantation.

The clinical data submitted in the PMA indicate that:

- The occurrence of post-operative renal dysfunction (i.e., oliguria, acute renal failure, and abnormal renal function) observed in Sealant and Control patients were 9/103 (8.7%) and 2/58 (3.4%), respectively.

  While 3/9 Sealant and 1/2 Control subjects who had an adverse event related to renal function also had pre-existing renal disease, severe adverse renal events occurred in 5/9 Sealant and 1 / 2 Control subjects. Considering the information on renal adverse events presented in your Executive Summary (i.e., page 31), the patient population in this study and the composition of ProGel Surgical Sealant, please discuss the clinical significance of these findings and the possibility that these events were device-related.

3. In the randomized (2:1 ratio) controlled, multi-center study in which 103 patients were treated with ProGel Surgical Sealant and 58 received Control treatment:

Summary of Effectiveness Outcomes
Ref: p4538 & pages 47-62, Appendix 3 Amendment 6,

	ProGel Surgical Sealant (n=103)	**Control (n= 58)**	**p-value**
Subjects who remained air leak-free through the 1 MFU visit	36/103 (35%)	8/58 (14%)	0.005
Duration of POALs[1]			
Median	2.0	2.0	NS
Mean	4.7	3.6	
Duration of CT Placement[1]			
Median	5.0	5.0	NS
Mean	6.97	6.7	
Length of hospital stay[1]:			
Median	6.0	7.0	0.04
Mean	7.4	9.3	
Incidence of partial expansion at 30 days	32 (33.3%);	12 (22.6%)	NS

[1] Ten (10%) Sealant and one (2%) Control subjects were discharged with a Heimlich valve

Do the data presented in P010047 demonstrate that there is reasonable assurance of effectiveness (i.e., in a significant portion of the target population, the use of ProGel Surgical Sealant's for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings will provide clinically significant/meaningful results)?

4. Does the P010047 safety profile of ProGel Surgical Sealant use compared to control adequately demonstrate a reasonable level of risk of adverse events, illness or injury associated with the use of ProGEL Surgical Sealant for its intended uses and conditions of use?